Real-time Seizure Detection System using Multiple Single-Neuron Recordings

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Abstract- **Approximately 20% of people diagnosed with epilepsy cannot be treated effectively. Consequently, there exists a significant need for alternative types of treatment. To aid in the effort of solving this problem, we developed a prototype system to detect changes in neural activity prior to the onset of a seizure. This system can be used as warning device or as part of a large system to terminate seizures in their initial stages via drug administration or nerve stimulation. The detection algorithm used data collected from intracranial electrodes. The waveforms were filtered and amplified to identify single neuron action potentials. The time of occurrence of each action potential for each neuron was then passed to a preprocessor algorithm that summed the data into 50ms time bins. Sliding windows consisting of 128 bins for each neuron were cross-correlated. The results were summed and the variance of the cross-correlation was used as a measure of global neuron correlation. The algorithm was implemented in a PC board and tested in rats treated with pentylenetetrazol (PTZ) a known seizure inducing drug. The system was 100% effective at detecting seizures approximately 4.6 seconds before seizure onset and had a false positive rate of 0.3%.**

Keywords – **epilepsy; rat; neural system; neural control**

I. INTRODUCTION

Approximately 20% of patients with epilepsy do not respond to traditional treatment methods. Since the occurrence of seizures is spontaneous, often with no warning, a method for reliably anticipating the onset of a seizure would provide an opportunity for therapeutic intervention. Many investigations have attempted to use EEG data from surface or intracranial electrodes to capture dynamic changes in the neural signals that predict the onset of a seizure [1-2]. However, the EEG signals reflect global changes in neural activity and are often recorded far from the focal source of the seizure. Attempts to use these signals to anticipate the onset of a seizure have been mixed with generally low detection rate and high false positive rates [3].

Recent studies using multiple EEG recording sites suggest that there are unique characteristics of the epileptogenic network that can be detected prior to the onset of a seizure [4-5]. The EEG data just prior to the onset of a seizure show changes in the dynamic structure of the neural activity and these changes are sufficient to predict the onset of a seizure [6]. While these results are promising, additional study is necessary to create a reliable and accurate system for therapeutic use.

The underlying theory behind these detection algorithms is that the complexity of the neural signals decreases prior to the onset of a seizure [7]. By calculating complexity measures of the EEG waveform, dynamic changes can be detected. However, the reason for a decrease in complexity of the EEG signal is that neural activity becomes synchronous as the seizure develops. The EEG signals are measures of global neural activity and as such are only a reflection of this increased synchrony. Therefore, we propose to use signals recorded from single neurons to detect this synchrony. The advantages of using single neuron activity are threefold.

First, the single neuron behavior at the seizure focal point represents the source of the EEG signal of interest for seizure detection. Second, measuring the synchrony of single neuron activity is computational more efficient than calculating complexity measures of the EEG waveform. Third, theoretically, the neural synchrony can be detected in the single neuron data long before the dynamic changes in the EEG are detectable.

We have developed a method for detecting pre-seizure activity in rats by monitoring single neuron activity. It is well known that the EEG signal is a reflection of the underlying single-neuron activity. By recording neural activity from multiple, single-neurons, our results suggest that local changes in neural firing patterns can be detected and used to predict the onset of a seizure

II. METHODS

A. Chronic implantation of electrodes

Two adult female Long-Evans rats were implanted with an eight channel electrode array to record single-neuron activity. All procedures and experiments were conducted in compliance with Drexel University animal use policies and were approved by the Drexel University Institutional Animal Care and Use Committee. The electrodes were implanted bilaterally into the temporal lobe of each rat. The rats were anesthetized with nebutal (50mg/kg). Small craniotomies were made in the skull over the implant site and the electrodes were slowly lowered into the neural tissue to a depth of 2.5 mm. Recordings were made throughout the

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Abstract

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implantation process to access electrode function. Small screws in the skull were used to anchor the electrodes, which were then cemented into place creating an electrode cap.

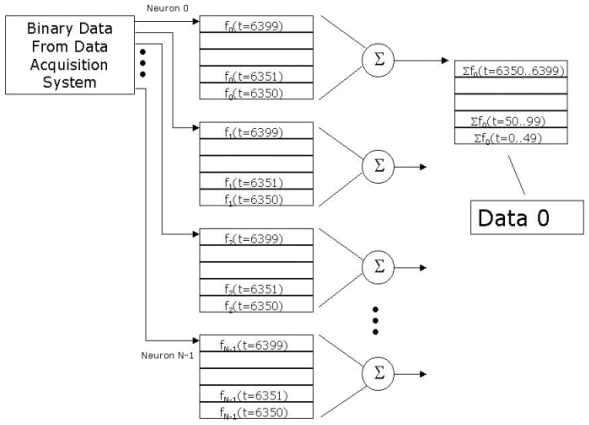

Figure 1 Binary data from the MNAP system that represented the time of occurence of action potentials for each single neuron were stored in registers. Then the number of action potentials during a 50 ms interval were summed to create a single bin. 128 bins representing 6.4 seconds of data were collected and represented a single window for cross correlation analysis.

B. Data Collection

After two weeks, the rats were placed in a recording chamber and a headstage was connected to the electrode cap (Plexon, Inc., Dallas TX). The headstage transmitted neural signals from the rat to a Multi-Neuron data Acquisition Program (MNAP) that filtered and amplified the signal and discriminated single neuron action potentials from the analog signal. The times of occurrence of action potentials for each neuron were stored.

During a recording session, five minutes of baseline data were collected and then the rats were given an injection of PTZ (40mg/kg). This dose of PTZ induced generalized seizure activity for up to 3 hours [8-9]. Continuous recording were made during the 3 hours post-injection.

C. Behavioral Analysis

During data acquisition, the animals were videotaped to monitor their behavior and to evaluate the onset of seizures. The videotapes were scored for each 30 msec frame as seizure or no-seizure as evaluated by the clonic jerking of the body and forelimbs. Half of this data was used to generate detection algorithm and the other half was used to test the algorithm.

III. Results

A Preprocessing

The raw data from the MNAP system consisted of M channels where M is the number of single neurons recorded per session. Data were represented at one millisecond (1 ms) time intervals and the occurrence of an action potential during that millisecond was represented as a 1 otherwise it was a zero. The seizure detection unit summed the binary data over a 50 msec interval to create a single bin whose value represented the number of times the cell fired an action potential during that 50 ms interval (Fig. 1). A window was created that collected 128 bins, representing 6.4 seconds of data for each channel.

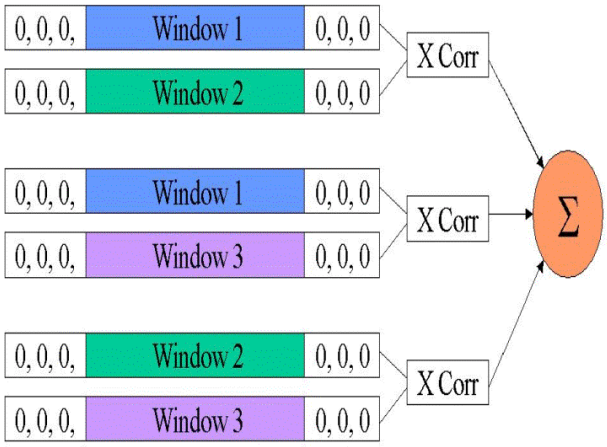

Figure 2 Schematic representation of the cross correlation method used to analyze the single neuron data and evaluate a seizure. This figure illustrates the pair-wise cross correlation for three neurons.

B. Signal Processing Solution

The M windows, one for each neuron recorded, were pairwise cross correlated (Fig. 2) to create M choose 2 cross-correlation vectors. The cross correlation vectors were created by holding the window for the reference neuron stationary while sliding each of the 128 bins of the window of the correlating neuron past the reference window one bin at a time. For each t, -127<t<128, the value of each bin in the reference window is multiplied by the adjacent window of the correlating neuron window. Then t was incremented and the correlating neuron window shifted one bin over the reference neuron window. The process was repeated until the correlated window had moved completely past the reference neuron window. For each bin of the reference window, the product of the reference bins and the correlation bin are added to the result from previous calculation resulting in a correlation vector with length 2t, t=128. The correlation vector for all pair wise correlation were averaged and the standard deviation at t=0 was used as a measure of synchrony. This synchrony measure was used to determine if a seizure was about to occur (Fig. 3).

When the value of the standard deviation for each bin was plotted, there was a clear separation between synchrony measures during seizure and nonseizure activity. A critical value for the synchrony measure was selected so that 100% of the seizures had a standard deviation less than this critical value and only 0.3% of the non-seizure bins had a standard deviation less than this critical value (Fig. 4). When the standard deviation reached the critical value (72 in Fig. 4), 100% of the bins that occurred during the seizure had a

standard deviation below this value while 99.7% of the bins recording during the baseline period were above this value (Fig. 4B). Therefore, using this critical value as a cut-off for evaluating the state of the animal, 100% of the seizures were detected and only 0.3% of the non-seizure bins were incorrectly labeled as seizures.

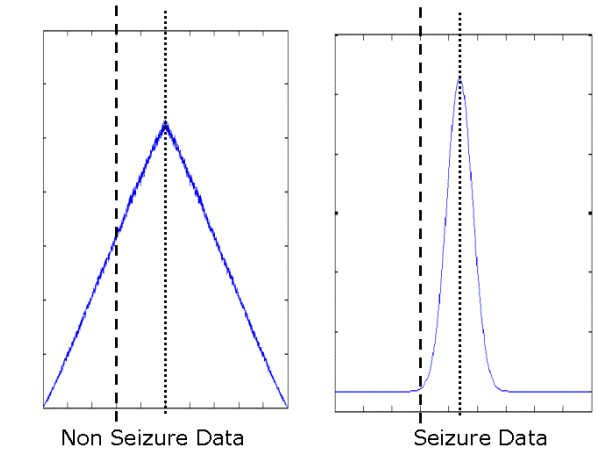

Figure 3 Diagram showing changes in the shape of the correlation function during non-seizure events and during seizure events. The dotted line is the peak of the correlation (representing time 0) while the dotted line represents one standard deviation away from the mean. The value of the correlation function one standard deviation away from the mean was used to determine whether seizure activity was present.

Next, we used this synchrony measure to predict seizures. The second half of the data, set aside for testing our method, was used. The continuous data recorded during sessions when the animal had been injected with PZT was streamed into our detection algorithm. The cross-correlation was recomputed for each new 50 msec bin acquired. Under these conditions, not only was the system able to detect 100% of the seizure episodes, but the system also registered a period of synchrony just prior to the seizure onset. This synchrony created a standard deviation of the cross-correlation below the critical value, suggesting a seizure was taking place. However, the standard deviation of the cross-correlation was actually below the critical value approxiametely 4.6 seconds before the onset of the seizure. These results suggest that this synchrony measure could be used to predict the onset of a seizure.

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III. Discussion

Cross-correlation analysis of multiple-channel, single-neuron data was used to detect neural activity associated with the onset of a seizure. Pair-wise correlations between each neuron during 6.4 second time window were averaged and the standard deviation of this measure was used to detect neural activity associated with the onset of the seizure. This method was able to detect 100% of the seizures and had a false positive rate of 0.3%. On average, this method was able to detect seizures 4.6 seconds before the onset of behavior manifestation.

The procedure outlined here represents a viable method for detecting neural activity associated with the onset of a seizure so that subsequent neural stimulation or drug delivery can be implemented to prevent the seizure onset. We have begun

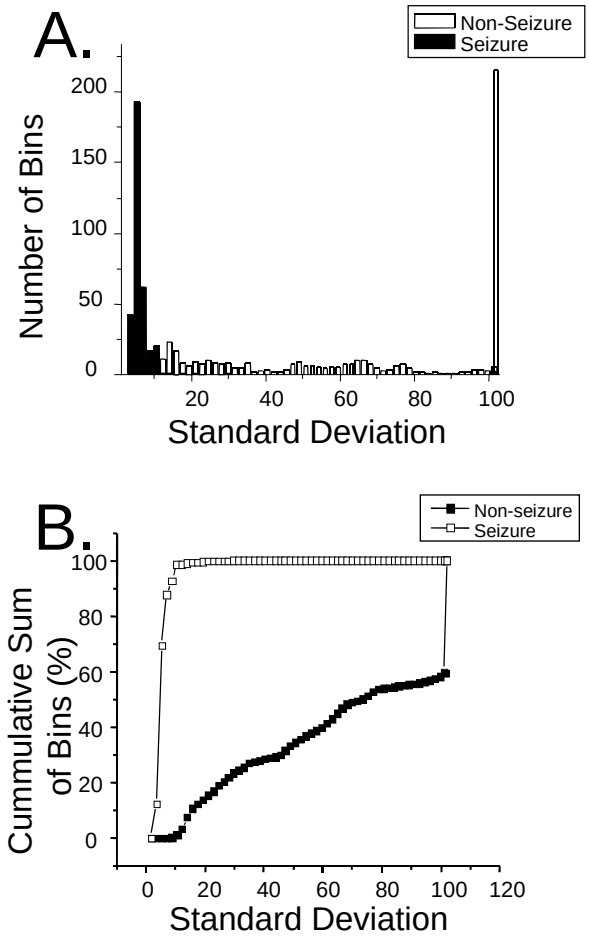

Figure 4 A. Histograms showing the number of bins in the correlation matrix with a given standard deviation value (as percent of the mean). Solid bars indicate bins during a seizure and open bars represent non-seizures bins. B. Cumulative sum of the number of bins with a given standard deviation. The open squares curve represents the cumulative sum of the number of seizure bins with standard deviations smaller than the current value. The solid squares curve represents the number of non-seizure bins with a standard deviation less than the current value. A critical value can be selected that represents the value of the standard deviation for which the value of all seizure bins are smaller and 99.7% of the non-seizure bins are greater.

trials in our lab to test the real-time implementation of this device with neural stimulation to prevent seizures. We expect results from these analyses before publication.

Of course, since this method requires implanting intracranial electrodes, the method is only appropriate for those patients for which other methods do not work and who

have already been recommended for intracranial electrodes to evaluate seizures.

The advantage of this method is that the critical value for synchrony can be adjusted on a per-patient basis such that no seizures are missed. The trade-off will then be the number of false positives allowed. Generally, there is very little adverse effect of false positives. However, the ability to detect 100% of the seizures may be critical for the patient. This will allow the patient to rely on the warning and, at the least, get to a safe place before the onset of the seizure. A device for which the patients knows will miss seizures, will afford the patient little relief from the constant concern of a spontaneous seizure occurring while the patient is engaged in an important activity such as driving a car.

In addition, this detection algorithm can be computed in real-time and, on average, detects the seizure 4.6 seconds before onset of physical manifestations. This could allow enough advanced warning for the patient to retreat to a safe environment or for a device to be activated to suppress the seizure [10]. For example, commercial devices have been developed that use nerve stimulation to prevent seizures. These devices use chronic, intermittent stimulation to prevent the onset of a seizure.

REFERENCES

[1]Webber, W.R.S., Lesser, R.P., Richardson, R.T., Wilson, K., An approach to seizure detection using an artificial neural network, Electroencephalography and Clinical Neurophysiology, 98, 250, 1996.

[2] Osorio, I., Frei, M.G., Wilkinson, S.B., real-time automated detection and quantitative analysis of seizures and short-term prediction of clinical onset, Epilepsia, 39(6), 615, 1998.

[3] Gabor, A.J., Seizure detection using a self-organizing neural network: validation and comparison with other detection strategies, Electroencephalography and Neurophysiology, 107, 27, 1998.

[4] Le Van Quyen, M., Martinerie, J., Baulac, M., Barela, F., Anticipating epileptic seizures in real time by a non-linear analysis of similarity between EEG recordings, NeuroReport, 10(10) 2149, 1999.

[5] Qu, H., Gotman, J., A seizure warning system for long-term epilepsy monitoring, Neurology, 45, 2250, 1995

[6] Schiff, S.J., Jerger, K., Duong, D.H., Chang, T., Spano, M.L., Ditto, W.L. "Controlling chaos in the Brain", *Nature*, 370, 615,. 1994.

[[7] Le Van Quyen, M., Adams, C., Martinerie, J., Baulac, M., Clemenceau, S., Varela, Spatio-temporal characterizations of non-linear changes in intracranial activities prior to human temporal lobe seizures, European Journal of Neuroscience, 12, 2124, 2000.

[8] Becker, A., Krug, M., Schröder, H. "Strain differences in pentylenetetrazol-kindling development and Subsequent potentiation effects", *Brain Research*, 763, 87, 1997.

[9] Fanselow, E.E., Reid, A.P., Nicolelis, M.A.L., Reduction of pentylenetetrazole-induced seizure activity in awake rats by seizure-triggered trigeminal nerve stimulation, J. of Neurosci, 20(21), 8160, 2000.

[10] Uthman, B.M., Wilder, B.J., Hammond, E.J., Reid, S.A., Efficacy and safety of vagus nerve stimulation in patients with partial complex seizures, Epilepsia, 31, S44, 1980.